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ORIGINAL REPORT

Accelerated Approval of Cancer Drugs: Improved Access to Therapeutic Breakthroughs or Early Release of Unsafe and Ineffective Drugs?

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ABSTRACT

Purpose
Accelerated approval (AA) was initiated by the US Food and Drug Administration (FDA) to shorten development times of drugs for serious medical illnesses. Sponsors must confirm efficacy in postapproval trials. Confronted with several drugs that received AA on the basis of phase II trials and for which confirmatory trials were incomplete, FDA officials have encouraged sponsors to design AA applications on the basis of interim analyses of phase III trials.

Methods
We reviewed data on orphan drug status, development time, safety, and status of confirmatory trials of AAs and regular FDA approvals of new molecular entities (NMEs) for oncology indications since 1995.

Results
Median development times for AA NMEs (n = 19 drugs) and regular-approval oncology NMEs (n = 32 drugs) were 7.3 and 7.2 years, respectively. Phase III trials supported efficacy for 75% of regular-approval versus 26% of AA NMEs and for 73% of non–orphan versus 45% of orphan drug approvals. AA accounted for 78% of approvals for oncology NMEs between 2001 and 2003 but accounted for 32% in more recent years. Among AA NMEs, confirmatory trials were nine-fold less likely to be completed for orphan drug versus non–orphan drug indications. Postapproval, black box warnings were added to labels for four oncology NMEs (17%) that had received AA and for two oncology NMEs (9%) that had received regular approval.

Conclusion
AA oncology NMEs are safe and effective, although development times are not accelerated. A return to endorsing phase II trial designs for AA for oncology NMEs, particularly for orphan drug indications, may facilitate timely FDA approval of novel cancer drugs.

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INTRODUCTION

Accelerated approval (AA) regulations were established by the US Food and Drug Administration (FDA) in 1992.[1] These regulations are designed to improve access to therapeutics for life-threatening diseases by allowing sponsors to begin marketing relevant drugs on the basis of trials that identify improvements in surrogate outcomes, such as response rate or progression-free survival, that are reasonably likely to predict clinical benefit.[1] A 1996 initiative from the Office of the President of the United States expanded use of the AA process for cancer therapies by allowing sponsors to seek AA for oncology new molecular entities (NMEs).[1,2] The regulation requires sponsors to conduct confirmatory studies to verify clinical efficacy.[2,3] An important feature of AA is that the registration trial can be phase II or phase III in design. AA designation of NMEs for serious medical illnesses differs in intent from the fast track designation for drugs that are first-in-class (wherein sponsors are allowed to submit the application for FDA approval in parts) and from the priority review for drugs that address unmet medical needs (wherein the FDA agrees to review the application in 6 months versus the standard 10-month time period).

In 2003, the US Food and Drug Administration requested that the Oncologic Drugs Advisory Committee (ODAC) review difficulties faced by sponsors

of AA oncology NMEs who had failed to complete required confirmatory trials (Fig 1).[4] Drugs discussed at this meeting had received AA on the basis of surrogate clinical outcome findings reported in phase II trials. In a journal publication, but not as formal agency guidance, FDA authors summarized recommendations from this meeting, which advised sponsors to consider adding sites to confirmatory phase III trials in countries where access to new cancer drugs is limited.[5] In 2005, a second ODAC meeting reviewed continuing difficulties faced by sponsors who had attended the 2003 ODAC meeting.[6] The consensus was that sponsors had conscientiously implemented recommendations from the prior meeting, yet recruitment to confirmatory phase III trials continued to be difficult. The FDA advised sponsors that future AA applications should preferentially be based on interim analyses of phase III (rather than phase II) trials, thus obviating the need for recruitment to additional confirmatory phase III trials.[6-8] Also, FDA staff advised the ODAC and sponsors that single-arm, phase II studies are interpretable only for the purposes of AA applications in the setting of refractory disease. In contrast, interim analyses of phase III trials could support AA in a broad range of settings, and additional follow-up of these trials could provide evidence of clinical benefit.

Opinions on the success of the AA regulation vary. In the 2004 publication, Dagher et al[5] concluded that AA had been successful in facilitating rapid evaluation of novel agents to patients with cancer.[5] However, Congressman Ed Markey has voiced concern that sponsors have abused the AA process by failing to confirm efficacy or by promoting unsafe drugs. In 2007, Congress passed legislation to allow the FDA to impose fines on sponsors and to limit drug distribution if postmarketing commitments are not completed.[9] Another concern is that obtaining AA, apparently, has become more difficult recently.[10,11] Proposed legislation would shorten FDA review times for sponsors seeking AA to 4 months from the current 6- to 10-month time period in an effort to shorten the development time of oncology NMEs.[12]

We review the experience to date with AA for oncology NMEs. We evaluated whether AA for oncology drugs facilitated rapid access to effective agents; whether confirmatory trials confirming efficacy of these drugs are completed; and whether safety concerns are identified after AA is granted. We also evaluated temporal changes in the frequency with which oncology NMEs received approval with regular-approval versus AA mechanisms.

METHODS

The first AA for a cancer indication was granted in May 1995. We reviewed information on new drug applications for oncology NMEs approved by the FDA between 1995 and 2008. Oncology drugs that previously received FDA approval for another indication or for supportive care indications were excluded. Data sources included clinical trial reports available under the Freedom of Information Act for new drug applications, transcripts of ODAC meetings in 2003 and 2005 on AA, efficacy and safety information available to the public on the FDA Web site, and package inserts for information on oncology NMEs that received AA and regular approval.[4,6,13] Details of trials that supported AA, regular approval, or conversion from AA to regular approval were obtained from the Center for Drug Evaluation and Research database.[14] Cancer indications are designated as orphan drug indications if the United States prevalence is fewer than 200,000 persons and if the FDA grants this status.[15,16] Drug development times, operationally defined as the number of months between granting of an investigational new drug (IND) authorization and FDA marketing approval, were based on information obtained from pharmaceutical sponsors or the FDA. For 25% of the NMEs, the manufacturers reported that IND authorization dates were proprietary.

For analyses of FDA approvals that were based on calendar year, we defined three distinct time periods. The first time period, 1995 to 2000, encompassed applications for FDA approval of oncology NMEs in which a development time line had been established before the 1996 Presidential Initiative that established the AA process for oncology drugs. The second time period, 2001 to 2003, encompassed applications for FDA approvals of oncology NMEs in which the development time line was likely to have been established after the 1996 Presidential Initiative. The third time period, 2004 to 2008, encompassed applications for FDA approvals of oncology NMEs in which the development time line was influenced in large part by the recommendations of the FDA and the ODAC at the 2003 ODAC meeting on AA (Fig 1).

Statistical analyses involved comparisons of median values and proportions for characteristics of trials that supported AA and regular approval. We used Kaplan-Meier curves and a Cox model to evaluate time to fulfillment of subpart H requirements (ie, confirmation of clinical efficacy for drugs that initially received AA on the basis of improvements in surrogate outcome measures) through February 15, 2009. Stata version 10.1 (Stata, College Station, TX) was used.

RESULTS

Since the first AA for an oncology (supportive care) indication was granted in 1995, 51 NMEs have received FDA approval for cancer

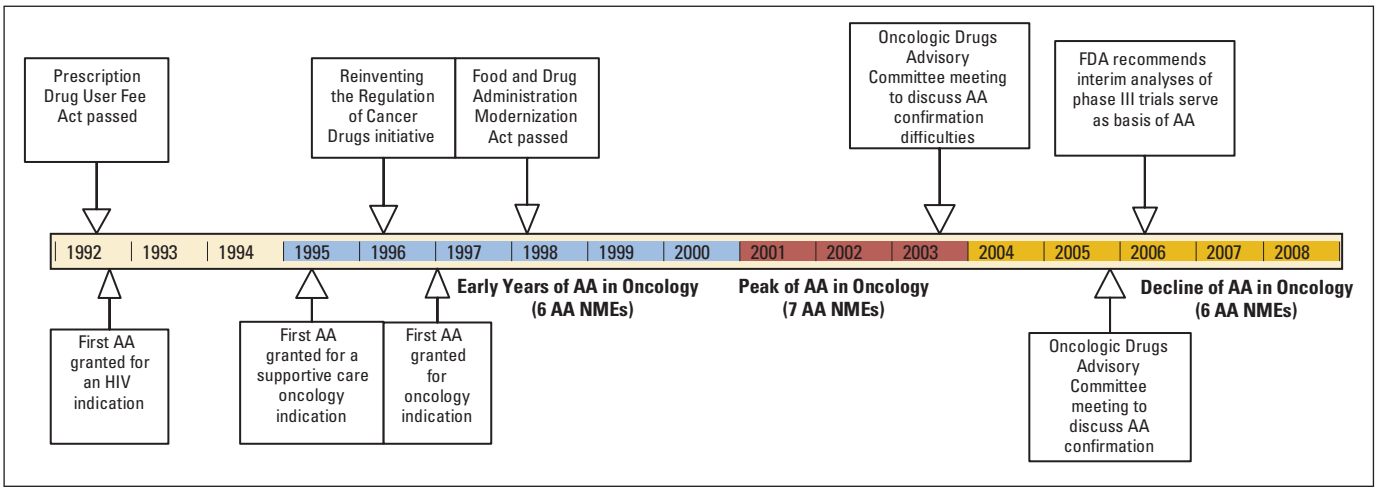

Fig 1. Time line of US Food and Drug Administration (FDA) regulatory events related to accelerated approval (AA). NME, new molecular entity.

therapeutic indications: 32 with regular approvals and 19 with AAs (Tables 1 and 2). The first AA for a therapeutic oncology indication, for docetaxel for the treatment of metastatic breast cancer, was in 1996. AAs accounted for 37% of oncology NMEs that received FDA approval between 1995 and 2008 and accounted for 26% during 1995 to 2000 (ie, mean of one AA per year); they accounted for 78% during 2001 to 2003 (ie, mean of 2.3 AAs per year); and they accounted for 32% during 2004 to 2008 (ie, mean of 1.2 AAs per year; Table 3; Fig 2).

Thirty-one oncology NMEs received FDA approval for treatment of solid tumors: 66% of the regular approvals and 47% of the AAs for oncology NMEs. Twenty-three regular approvals and AAs were for treatment of common solid tumors, including cancer of the breast (n = 10 and n = 2, respectively), prostate (n = 4 and n = 0, respectively), lung (n = 1 and n = 1, respectively), and colorectum (n = 1 and n = 4, respectively). For less-common solid cancers, seven oncology NMEs received regular approval (for cancers of the kidney, cervix, esophagus, or bladder and mesothelioma) and one received AA (for renal cell cancer). Overall, 53% of oncology NMEs that received regular approval and 63% of oncology NMEs that received AA were for orphan drug indications.

Phase III trials supported efficacy findings for 75% of regular-approval versus 26% of AA oncology NMEs. Response rates or times to progression were the primary surrogate end points in registration trials for 89% and 11% of the AA oncology NMEs, respectively. Non–orphan drug indication NMEs were 1.5-fold more likely than orphan drug indication NMEs to receive initial FDA approval on the basis of phase III studies (73% *v* 45%, respectively). The median number of patients included in studies that supported regular versus AA approval was 1.5-fold greater for non–orphan drug indications (469 *v* 304 patients, respectively) and was 1.3-fold greater for orphan drug indications (201 *v* 152 patients, respectively).

The median development times for oncology NMEs that received AA and for those that received regular approval were 7.3 years and 7.2 years, respectively. Between 2001 and 2003, the median development time was slightly shorter for NMEs approved for non–orphan drug cancer indications (8.1 years) than for orphan drug cancer indications (8.9 years). Since 2004, median development times were slightly longer for orphan drug (7.8 years) versus non–orphan drug cancer indications (5.7 years; Table 4).

Eleven (63%) of 19 oncology NMEs granted AA have had clinical benefit confirmed in subpart H trials and have been granted regular

Table 1. Oncology New Molecular Entities That Received Accelerated FDA Approval From 1995 Through 2008

Drug	Indication	Date of FDA Approval	Primary End Point	Trials That Support Approval		No. of Patients Included in Trials	Subpart H Completion Date
				Phases	No. of Trials		
Orphan drug indication							
Denileukin diftitox	Cutaneous T-cell lymphoma	2/5/1999	RR	I/II, III		106	10/15/2008
Temozolomide	Anaplastic astrocytoma/high-grade glioma with radiation therapy	8/11/1999	RR	II		162	3/15/2005
Gemtuzumab	$CD33^+$ AML	5/17/2000	RR	II	3	142	Pending
Alemtuzumab	B-cell CLL, treated with alkylating agents, failed fludarabine	5/7/2001	RR	II		93	9/19/2007
Imatinib	Ph-positive CML in AP, CP after failure of IFN-α, blast crisis	5/10/2001	RR	II	3	1027	12/8/2003
Ibritumomab tiuxetan	Relapsed, refractory, low-grade follicular or transformed NHL	2/19/2002	RR	II, III		197	Pending
Bortezomib	Refractory multiple myeloma	5/13/2003	RR	II	2	256	3/25/2005
Tositumomab	Rituximab-naïve follicular NHL	6/27/2003	RR	II		40	9/19/2007
Cetuximab	EGFR-positive metastatic colorectal cancer in second-line combination with irinotecan	2/12/2004	RR	II	3	524	10/2/2007
Clofarabine	Pediatric ALL	12/28/2004	CR	I, II	2	86	Pending
Nelarabine	T-cell ALL/lymphoma	10/28/2005	RR	II	2	67	Pending
Nilotinib	CP and AP Ph-positive CML	10/29/2007	RR	II		337	Pending
Non–orphan drug indication							
Docetaxel	Metastatic breast cancer	5/14/1996	RR	II	3	134	6/22/1998
Irinotecan	Metastatic colorectal cancer	6/14/1996	RR	II	3	304	10/22/1998
Capecitabine	Metastatic breast cancer	4/30/1998	RR	II		163	9/7/2001
Oxaliplatin	Metastatic colorectal cancer	8/9/2002	RR, TTP	III		463	1/9/2004
Gefitinib	Single-agent therapy for refractory NSCLC	5/5/2003	RR	II		142	6/17/2005
Sunitinib	Advanced renal cell carcinoma	1/26/2006	TTP	III		312	2/2/2007
Panitumumab	Third-line treatment of EGFR-expressing metastatic colon cancer, progression after other chemotherapy	9/27/2006	PFS	III		463	Pending

Abbreviations: FDA, US Food and Drug Administration; RR, response rate; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; CML, chronic myelogenous leukemia; AP, acute progression; CP, chronic progression; IFN, interferon; NHL, non-Hodgkin's lymphoma; EGFR, epidermal growth factor receptor; CR, complete response; Ph-positive, Philadelphia chromosome positive; TTP, time to progression; NSCLC, non–small-cell lung cancer; PFS, progression-free survival.

Table 2. Oncology New Molecular Entities That Received Regular FDA Approval From 1995 Through 2008

Drug	Indication	Date of FDA Approval	Primary End Point	Trials That Support Approval		No. of Patients Included in Trials
				Phase	No. of Trials	
Orphan drug indication						
Porfimer	Palliative care esophageal cancer	12/27/1995	RR	II		236
Toremifene citrate	Treatment of advanced breast cancer in postmenopausal women	5/29/1997	RR, TTP	III	3	1,175
Rituximab	First-line treatment DLBC CD20$^+$ NHL	11/26/1997	RR	II, III		166
Valrubicin	Intravesical therapy of BCG-refractory carcinoma of the bladder	9/25/1998	CR	II		90
Alitretinoin	Cutaneous lesions in patients with AIDS-related Kaposi's sarcoma	2/2/1999	RR	III	2	402
Epirubicin hydrochloride	Early-stage breast cancer that has spread to lymph nodes	9/15/1999	PFS	III		716
Exemestane	Adjuvant treatment ER-positive breast cancer, postmenopausal	10/21/1999	RR	III		769
Bexarotene	Cutaneous manifestations of cutaneous T-cell lymphoma	12/29/1999	Physician's assessment of clinical response, RR	II/III	2	152
Arsenic trioxide	Acute promyelocytic leukemia, chemotherapy refractory or recurred	9/25/2000	CR	I, II		52
Pemetrexed	Malignant pleural mesothelioma	2/2/2004	PFS	III		448
Sorafenib tosylate	Advanced renal cell carcinoma	12/20/2005	OS, PFS	II, III		769
Lenalidomide	MDS	12/27/2005	Red blood cell transfusion independence	II		148
Decitabine	MDS	5/2/2006	RR	III		170
Dasatinib	Ph-positive ALL with resistance or intolerance to prior therapy	6/28/2006	HR	II		36
Vorinostat	Refractory cutaneous T-cell lymphoma	10/6/2006	RR	I, II	5*	107
Temsirolimus	Advanced renal cell carcinoma	5/30/2007	OS	III		626
Bendamustine hydrochloride	CLL	3/20/2008	RR	III		201
Non–orphan drug indication						
Bicalutamide	Anti-androgen advanced prostate cancer	10/4/1995	OS	III	2	320
Anastrozole	Treatment for breast cancer in postmenopausal women	12/27/1995	RR	III	2	564
Gemcitabine hydrochloride	First-line treatment of metastatic breast cancer with paclitaxel	5/15/1996	TTP, RR	III		529
Topotecan hydrochloride	Stage IVB recurrent or persistent carcinoma of the cervix in combination with cisplatin	5/28/1996	PR, CR	II, III		226
Nilutamide	Treatment of metastatic prostate cancer	9/19/1996	PFS	III		457
Letrozole	Adjuvant treatment early breast cancer, postmenopausal women	7/25/1997	TTP	II		907
Trastuzumab (Herceptin)	Metastatic HER2-positive breast cancer	9/25/1998	TTP	II, III		469
Triptorelin pamoate	Palliative treatment of advanced prostate cancer	6/15/2000	Achievement and maintenance of medical castration	III		277
Fulvestrant	Metastatic ER-positive breast cancer in postmenopausal women	4/25/2002	RR, TTP	III		851
Abarelix	Palliative treatment advanced symptomatic prostate cancer	11/25/2003	Achievement and maintenance of medical castration	II, III	4†	1,171
Bevacizumab	First-line treatment for metastic colon cancer	2/26/2004	OS	III		450
Azacitidine	Myelodysplastic syndrome subtypes	5/19/2004	RR	I, II	5*	319
Erlotinib hydrochloride	Locally advanced or metastatic NSCLC that has failed another chemotherapy	11/18/2004	OS	III		731
Lapatinib ditosylate	Advanced or metastatic breast cancer, overexpression of HER2	3/13/2007	TTP	III		399
Ixabepilone	Metastatic or locally advanced breast cancer	10/16/2007	PFS	III		752

Abbreviations: FDA, US Food and Drug Administration; RR, response rate; TTP, time to progression; DLBC, diffuse large B-cell; NHL, non-Hodgkin's lymphoma; BCG, bacillus Calmette-Guerin; CR, complete response; PFS, progression-free survival; ER, estrogen receptor; OS, overall survival; MDS, myelodysplastic syndrome; Ph-positive, Philadelphia chromosome positive; ALL, acute lymphatic leukemia; HR, hormonal response; CLL, chronic lymphatic leukemia; PR, partial response; HER2, human epidermal growth factor receptor 2; NSCLC, non–small-cell lung cancer.

*No. of trials per phase: phase I, n = 3; phase II, n = 2.

†No. of trials per phase: phase II, n = 1; phase III, n = 3.

Table 3. Temporal Analysis of Regular Versus Accelerated FDA Approval for Oncology NMEs

Approval Characteristic	Approval Time Frame		
	1995-2000	2001-2003	2004-2008
AAs			
No. overall	6	7	6
No. per year	1.0	2.3	1.2
NMEs to receive AA, %	26	78	32
Median years from IND to approval	5.5	9.3	6.7
Drugs with phase II study as only basis	Capecitabine,* docetaxel,* irinotecan,* gemtuzumab, temozolomide*	Alemtuzumab,* bortezomib,* gefitinib,* imatinib,* tositumomab*	Cetuximab,* clofarabine, nelarabine, nilotinib
Drugs with phase III study as basis	Denileukin diftitox*	Ibritumomab tiuxetan, oxaliplatin*	Panitumumab, sunitinib*
Regular approval			
No. overall	17	2	13
No. per year	2.8	0.3	2.6
NMEs to receive regular approval, %	74	21	68
Median years from IND to approval	8.5	6.2	7.0
Drugs with only phase II studies for basis	Arsenic trioxide, letrozole, porfimer, valrubicin		Azacitidine, dasatinib, lenalidomide, vorinostat
Drugs with only phase III studies for basis	Alitretinoin, anastrozole, bexarotene, bicalutamide, epirubicin hydrochloride, exemestane, gemcitabine hydrochloride, nilutamide, rituximab, topotecan hydrochloride, toremifene citrate, trastuzumab, triptorelin pamoate	Abarelix, fulvestrant	Bendamustine, bevacizumab, decitabine, lapatinib ditosylate, erlotinib hydrochloride, ixabepilone, hydrochloride pemetrexed, sorafenib tosylate, temsirolimus

Abbreviations: FDA, US Food and Drug Administration; AA, accelerated approval; NME, new molecular entity; IND, investigational new drug.
*Sponsors have completed subpart H confirmatory trials.

approval. Subpart H trials were completed for 71% of oncology NMEs associated with non–orphan drug tumor indications versus 58% of NMEs associated with orphan drug cancer indications. The completed subpart H commitment trial for one drug, gefitinib, did not identify clinical benefit, and the application for marketing approval was withdrawn by the sponsor. Cox proportional hazard models indicated that, among NMEs that received AA, oncology NMEs in which FDA approvals were for orphan dug cancer indications were nine-fold less likely to confirm clinical benefit and to complete subpart H commitments than those in which FDA approval was for non–orphan drug indications (hazard ratio, 0.11; 95% CI, 0.02 to 0.63; $P < .01$). The median times between granting AA and granting regular approval were 2.1 years for orphan drugs indications and 3.7 years for non–orphan drug oncology indications (Table 4; Fig 3).

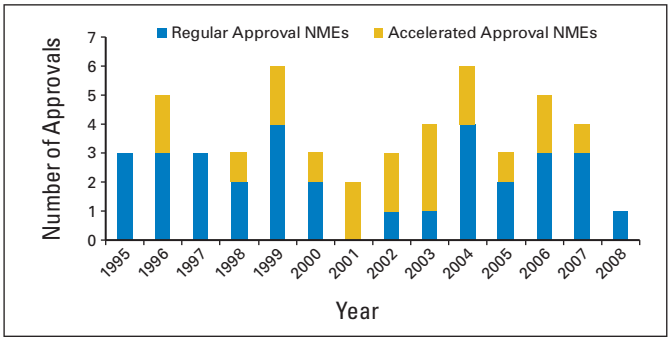

Fig 2. New molecular entities (NMEs) that received regular approval and accelerated approval (AA) from 1995 through 2008. Overall, 37% of oncology NMEs received AA. From 1995 to 2000, 26% received AA; from 2001 to 2003, 78% received AA; since 2004, 32% have received AA.

Of oncology NMEs that received AA, 63% are included in first-line cancer treatment regimens from the National Comprehensive Cancer Network (NCCN). Among NMEs that received FDA approval for non–orphan oncology indications, 83% that received AA and 91% that received regular approval are included in first-line regimens in NCCN clinical guidelines. Among NMEs that received FDA approval for orphan drug indications, 82% of regular-approval drugs and 33% of AA drugs are included in first-line regimens in NCCN guidelines.

After FDA approval, four black box warnings were added to package inserts for four (17%) oncology NMEs that had received AA, and three black box warnings were added to package inserts for two (9%) oncology NMEs that had received regular approval.

DISCUSSION

AA has facilitated access to many safe and highly effective NMEs that are indicated for cancer treatment. The FDA's published assessment on the first decade of the AA process for oncology drugs was that the regulation was very successful.[5] In May 2008, Richard Pazdur, MD, Director of the Office of Oncology Drug Products of the FDA, publicly stated that the AA regulation continues to be highly successful in

Table 4. Characteristics of Oncology New Molecular Entities Approved Between 1995 and 2008 by Accelerated or Regular FDA Approval and Orphan Drug or Non–Orphan Drug Indication

Characteristic	All Drugs (N = 51)	Approval Status		Orphan Drug Indication Status	
		AA (n = 19)	Regular (n = 32)	Orphan Drug Indication (n = 29)	Non–Orphan Drug Indication (n = 22)
Approval					
AA	37			41	325
Orphan drug indication	57	63	53		
Clinical development					
Phase III trials that support approval	57	26	74	45	73
Median No. of years from IND to approval					
Overall	7.3	7.3	7.2	8.4	7.2
1995-2000	7.2	5.5	8.5	8.5	5.5
2001-2003	8.8	9.3	6.2	8.9	8.1
2004-2008	7.0	6.7	7.0	7.8	5.7
Efficacy					
AA drugs converted from AA to regular approval	63	63		45	86
Included in first-line NCCN chemotherapy regimens	63	47	71	59	685
Included in first- and second-line NCCN chemotherapy regimens	88	84	91	93	82
Safety					
Black box at time of FDA approval	35	47	29	31	41
Black box added within 4 years of FDA approval	12	21	10	17	9

Abbreviations: FDA, US Food and Drug Administration; AA, accelerated approval; IND, investigational new drug; NCCN, National Comprehensive Cancer Network.

facilitating early access to large numbers of novel cancer drugs.[17] The findings of this report suggest an alternative, less positive, interpretation of the recent experience with AA. Although the AA process previously facilitated early access to new oncology drugs, it is now difficult to obtain FDA approval with the AA process. Overall, fewer oncology NMEs receive AA versus regular FDA approval in the recent time period. In interpreting these findings, several factors should be considered.

Increasing the threshold for granting AA for oncology NMEs would be appropriate if large numbers of these drugs are subsequently found to be ineffective. This does not appear to be the case. The majority of AA drugs that receive FDA approval for non–orphan drug indications (including docetaxel, sunitinib, irinotecan, capecitabine, and oxaliplatin) have had clinical benefit confirmed in subpart H trials, are included in first-line chemotherapy regimens from the NCCN, and represent important therapeutic breakthroughs. Similarly, many oncology NME drugs that received AA for orphan drug indications (including imatinib, bortezomib, alemtuzumab, temozolomide, and cetuximab) also represent important therapeutic breakthroughs, have had clinical benefit confirmed in subpart H clinical trials, are included in first- or second-line chemotherapy regimens from the NCCN, and have led to improved survival for large numbers of patients with cancer. As reported here, when confirmatory phase III trials for an AA oncology NME are not completed, the approved clinical indication is almost always an orphan drug indication (eg, pediatric T-cell leukemia). Patients with cancer who have these rare diagnoses are generally unwilling to participate in a randomized, phase III trial in which there is a high likelihood that they would not receive a novel agent that recently received AA.

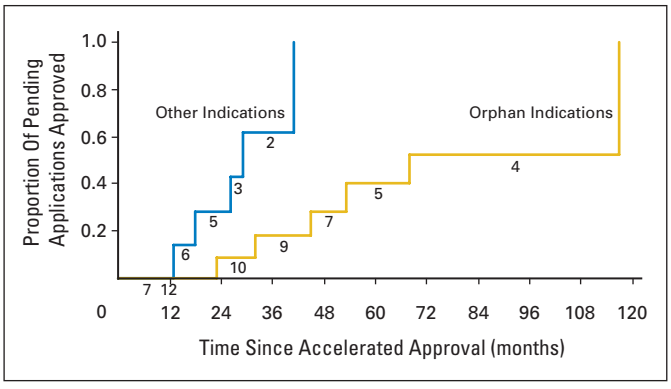

Fig 3. Kaplan-Meier curves for subpart H fulfillment for conversion from accelerated US Food and Drug Administration (FDA) approval to regular FDA approval for orphan drug versus non–orphan drug oncology indication. The numbers under each curve are the number of applications awaiting approval at the beginning of each time period for each type of indication.

A second proposed rationale for increasing the threshold for granting AA is that many of these drugs are ultimately found to be unsafe. This, too, does not appear to be the case—at least with respect to serious adverse drug reactions. Of four black box warnings added to package inserts associated with AA oncology NMEs, three were added more than 2 years after approval, which suggests that safety signals could not have been recognized during clinical trials. Of three warnings added to package inserts for regular-approval oncology NMEs, one (for rituximab) was added 1 year after FDA approval; another (for trastuzumab) was added within 2.5 years of FDA approval; and an additional black box warning for rituximab was added 9 years after approval. Previous data has shown that identification of severe adverse drug events occur at approximately equal rates in phase II and phase

III trials.[18] We note that more rapid adoption and growth in usage for regularly approved NMEs may account for some differences.

The original motivation for extending AA from the HIV setting to the cancer setting was that this process would facilitate early access to novel cancer agents. Shortened development times would result from sponsors applying for AA on the basis of analyses of surrogate clinical outcomes. In the early 2000s, the AA process appeared to be in full gear: 78% of oncology NMEs received AA versus regular approval. However, since 2004, only 32% of oncology NMEs have received AA versus regular approval. This change coincided with the failure of gefitinib to show clinical benefit in its confirmatory phase III trial and with concern expressed by FDA officials at ODAC meetings in 2003 and 2005 that sponsors were not completing agreed-on phase III trials designed to verify improvements in clinical outcomes for AA oncology NMEs. To facilitate timely enrollment in these trials, FDA officials encouraged sponsors to base initial AA applications on surrogate clinical outcomes reported in interim analyses of phase III trials rather than on final analyses that identified improvements in surrogate clinical measures for patients enrolled on phase II trials.[7] This recommendation mirrors FDA policy for HIV infection, but HIV infection is a limited, special case that does not represent the scope or complexity of the many diseases that have a malignant phenotype. The FDA approach to oncology drugs has been hampered by failure to systematically develop and analyze the range of biomarkers used in AA for validation as surrogate markers. Development of surrogate markers is a major thrust of modern therapeutic research, is the goal of several initiatives that include FDA participation, and is an area of pressing public health need to shorten time to market and to lessen costs.

Some study limitations should be noted. First, we focused on oncology NMEs intended as antitumor therapy and did not evaluate oncology drugs with AA that had previously received US Food and Drug Administration approval for other indications. These drugs differ from NMEs in that they are available, and frequently are reimbursed, for use in off-label settings; hence, AA designation is less relevant. Second, IND dates were used to derive estimates of development time. These dates were not available for 25% of the NMEs. However, characteristics of drugs for which IND dates were not available are similar to those for the entire population of oncology NMEs. Moreover, our metric of clinical development time, defined from IND date to approval, may not most accurately reflect clinical development in the human population. Pharmaceutical sponsors and the FDA should publicly disseminate information on IND dates and development times for all drugs and should allow patients and clinicians to have information on the duration of time that a drug was evaluated before it received FDA approval. Patients may be more willing to take AA medications with longer development times, and clinicians may be more willing to prescribe these medications. Third, information on new drug applications and characteristics of registration trials targeted for regular approval versus AA of oncology NMEs are not readily available. The possibility remains that, with maturation of AA experiences, regular FDA approval may be based on improvements in surrogate end points previously evaluated in AA applications. Finally, an alternative explanation for our findings is that fewer applications for AA have been made. Raw data on the number of applications for AA are not available. However, start-up pharmaceutical manufacturers have expressed their support for basing AAs for novel oncology NMEs on results of phase II trials, as the opportunity to achieve positive revenue in a short time frame is essential for their financial viability. They also note that the phase III trial design is particularly difficult for evaluating NMEs designed to treat orphan drug cancer indications, as the trials are expensive, require several-fold more patients with rare cancer diagnoses than phase II trials, involve larger numbers of clinical trial sites, require extensive collaboration of large numbers of physicians, and take longer to complete.

We conclude that the promise of AA (ie, shortening the time to approval and decreasing the resource burden of novel cancer drugs) is not being met, as evidenced by the similar development times, emphasis on phase III trial designs for both regular approval and AA, and the decreased number and percentage of oncology NMEs that receive AA since 2003. Going forward, for oncology NMEs associated with orphan drug indications, the phase II trial design may be optimal for identifying improvements in surrogate clinical outcomes, shortening development times, and lowering the bar for achieving AA. AA oncology NMEs in which clinical efficacy is not confirmed in phase III trials are usually associated with orphan drug indications, for which accrual to confirmatory phase III trials is particularly difficult. Punitive actions included in recent legislation, such as assessment of fines for failing to complete postapproval commitment studies, should be undertaken with caution for sponsors of drugs that receive AA for oncology indications. Although this approach also is proposed in the European Union, such an approach would represent a disincentive for sponsors to seek AA in the United States and ultimately would present a disservice to patients who have cancers associated with orphan drug indications.

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The author(s) indicated no potential conflicts of interest.

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